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From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 23 October 2000 (23.10.00)	To:  KILANDER, Annika Göteborgs Patentbyrå Dahls AB P.O. Box 606 S-182 16 Danderyd SUÈDE
Applicant's or agent's file reference 54660-59500	<b>IMPORTANT NOTIFICATION</b>
International application No. PCT/SE00/00384	International filing date (day/month/year) 28 February 2000 (28.02.00)

1. The following indications appeared on record concerning:

the applicant     the inventor     the agent     the common representative

Name and Address BERG, S., A. Albinhs Patentbyrå Stockholm AB P.O. Box 5581 S-114 85 Stockholm Sweden	State of Nationality	State of Residence
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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person     the name     the address     the nationality     the residence

Name and Address KILANDER, Annika Göteborgs Patentbyrå Dahls AB P.O. Box 606 S-182 16 Danderyd Sweden	State of Nationality	State of Residence
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3. Further observations, if necessary:

**The new agent's address on the Demand has been considered as a change under Rule 92bis. In case of disagreement, the International Bureau should be notified immediately.**

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  A. Karkachi  Telephone No.: (41-22) 338.83.38
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From the INTERNATIONAL BUREAU

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NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 23 October 2000 (23.10.00)	
International application No. PCT/SE00/00384	Applicant's or agent's file reference 54660-59500
International filing date (day/month/year) 28 February 2000 (28.02.00)	Priority date (day/month/year) 26 February 1999 (26.02.99)
Applicant HAEGGSTRÖM, Jesper, Z. et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

22 September 2000 (22.09.00)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  A. Karkachi  Telephone No.: (41-22) 338.83.38
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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PD53452PC	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE00/00384	International filing date ( <i>day/month/year</i> ) 28.02.2000	Priority date ( <i>day/month/year</i> ) 26.02.1999
International Patent Classification (IPC) or national classification and IPC7		
C 12 N 9/14, A 61 K 38/46 // A 61 P 29/00, A 61 P 037/08		
Applicant HAEGLSTRÖM, Jesper Z et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of \_\_\_\_\_ sheets.

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3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.09.2000	12.06.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer Telex 17978 PATOREG-S Yvonne Siösteen/EÖ Telephone No. 08-782 25 00

**I. Basis of the report****1. With regard to the elements of the international application:\*** the international application as originally filed the description:

pages \_\_\_\_\_, as originally filed

pages \_\_\_\_\_, filed with the demand

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

 the claims:

pages \_\_\_\_\_, as originally filed

pages \_\_\_\_\_, as amended (together with any statement) under article 19

pages \_\_\_\_\_, filed with the demand

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

 the drawings:

pages \_\_\_\_\_, as originally filed

pages \_\_\_\_\_, filed with the demand

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

 the sequence listing part of the description:

pages \_\_\_\_\_, as originally filed

pages \_\_\_\_\_, filed with the demand

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

**2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.**

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

 the language of a translation furnished for the purposes of international search (under Rule 23.1(b)). the language of publication of the international application (under Rule 48.3(b)). the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:** contained in the international application in written form. filed together with the international application in computer readable form. furnished subsequently to this Authority in written form. furnished subsequently to this Authority in computer readable form. The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished. The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.**4.  The amendments have resulted in the cancellation of:** the description, pages \_\_\_\_\_ the claims, Nos. \_\_\_\_\_ the drawings, sheet/fig \_\_\_\_\_**5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).\*\***

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\* Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,  
 claims Nos. \_\_\_\_\_

because:

the said international application, or the said claims Nos. \_\_\_\_\_  
relate to the following subject matter which does not require an international preliminary examination (specify):

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 11-15  
are so unclear that no meaningful opinion could be formed (*specify*):

As they relate to multiple dependent claims Rule 6.4(a) Search  
Guideline Chap VIII, pages 28, 4.1.

the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported  
by the description that no meaningful opinion could be formed.

no international search report has been established for said claims Nos. 11-15

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

the written form has not been furnished or does not comply with the standard.  
 the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

## 1. Statement

Novelty (N)	Claims	<u>16-18, 21-24, 26-27</u>	YES
	Claims	<u>1-10, 19-20, 25, 28-38</u>	NO
Inventive step (IS)	Claims	<u>16-18, 21-24</u>	YES
	Claims	<u>1-10, 19-20, 25-38</u>	NO
Industrial applicability (IA)	Claims	<u>1-10, 16-38</u>	YES
	Claims		NO

## 2. Citations and explanations (Rule 70.7)

The claimed invention relates to the isolated enzyme leukotriene A<sub>4</sub> (LTA<sub>4</sub>) hydrolase having the same three-dimensional structure as the enzyme found in nature. The structure of the enzyme is determined and the parameters defining the atoms are given. Several active sites are indicated. The claims also relate to a complex of LTA<sub>4</sub> with the inhibitor bestatin, thiolamine or hydroxic acid. A method for screening LTA<sub>4</sub> analogues using the enzyme is also claimed. By knowing the three-dimensional structure of the enzyme, it is possible to produce better and more selective inhibitors to LTA<sub>4</sub> hydrolase and to produce modified structures of the enzyme with better pharmacological properties.

Reference is made to the following documents:

- A Pir database, accession no. S65947, 1996-10-28, Mancini et al, Eur. J. Biochem. 231, pp65-71, 1995.
- B J.Mol.Biol., Volume 238, 1994, Tsuge et al., pp854-856.
- C Proc.Natl.Acad.Sci., Volume 88, 1991, Medina J.F. et al, Pp7620-7624.
- D Eur.J.Biochem, Volume 231, 1995, Blomster et al., pp 528-534.

The claimed enzyme is known and isolated. Its amino acid sequence is known from document A. A complex of the enzyme and bestatin is also disclosed in this document. LTA<sub>4</sub> hydrolase has been crystallised by Tsuge et al. (See document B). The three-dimensional structure of the enzyme is, however, not

.../...

**Supplemental Box**  
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

known from the prior art. The data according to table 9 describing the three-dimensional structure of the enzyme is considered novel. However, to characterize the known enzyme by new parameters such as the parameters for its three-dimensional structure or to indicate the active sites do not render the enzyme itself novel. Thus, the claimed enzyme and the complex with betastain lacks novelty.

Thus, claims 1-10 and 35 lack novelty and inventive step.

Claims 16-18 and 21-24 relate to a method for screening LTA<sub>4</sub> hydrolase analogues. The method uses the determined three-dimensional structure of the LTA<sub>4</sub> hydrolase as defined by the parameters shown in Table 9 to get analogues having increased and improved catalytic activity.

Claims 16-18 and 21-24 are novel and are considered to have an inventive step.

Claims 19,20,25 and 30-33 relate to a product produced by a method in another claim. These product by process claims are indefinite and also lack novelty. It cannot be excluded that the claims cover known products. A new method does not necessarily render novelty to a product.

Claims 19,20,25 and 30-33 lack novelty and inventive step.

Claims 26-27 relate to a method for engineering a protein using the knowledge of the structure of the enzyme. The method do not involve any novel feature nor is it restricted to the parameters of table 9. The method, therefore, is novel but is not considered to involve any inventive step.

Claims 26-27 are novel but lack inventive step.

It is known to purify and to crystallize LTA<sub>4</sub> hydrolase.

Claims 28-29 and 34 lack novelty and inventive step.

Claims 36-38 relate to known medical uses of the known enzyme in the area of inflammatory and allergic diseases.

Claims 36-38 lack novelty and inventive step.

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

Claims 19, 20, 25 and 30-33 do not disclose the invention in a sufficiently close manner. The products are not defined in a way which is clear and precise. See Article 6.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00384

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C12N 9/14, A61K 38/46 // A61P 29/00, A61P 037/08  
 According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C12N, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Pir database, accession no. S65947, 1996-10-28, Mancini J. A et al., "Cloning and characterization of the human leukotriene A(4) hydrolase gene"; Eur. J. Biochem. 231, 65-71, 1995  --	1-38
X	J. Mol. Biol., Volume 238, 1994, Hideaki Tsuge et al, "Crystallization and Preliminary X-ray Crystallographic Studies of Recombinant Human Leukotriene A4 Hydrolase Complexed with Bestatin" page 854 - page 856  --	1-38

 Further documents are listed in the continuation of Box C. See patent family annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

6 June 2000

26-06-2000

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM

Authorized officer

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00384

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Proc.Natl.Acad.Sci., Volume 88, 1991, Medina J. F. et al, "Leukotriene A4 hydrolase: Determination of the three zinc-binding ligands by site-directed mutagenesis and zinc analysis" page 7620 - page 7624	4,5
A	---	1-3,6-38
X	Eur. J. Biochem, Volume 231, 1995, Blomster, Martina et al, "Evidence for a catalytic role of tyrosine 383 in the peptidase reaction of leukotriene A4 hydrolase" page 528 - page 534	4,5
A	-----	1-3,6-38

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